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EXAMINER	
CAMPELL, B	
ART UNIT	**PAPER NUMBER**
1804	12

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DATE MAILED: 11/24/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☑ Responsive to communication filed on 9/25/95 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), ____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☑ Notice of References Cited by Examiner, PTO-892.
2. ☑ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☑ Notice of Art Cited by Applicant, PTO-1449. (2)
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☑ Claims 1-17 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☐ Claims _____ have been cancelled.

3. ☐ Claims _____ are allowed.

4. ☑ Claims 1-17 are rejected.

5. ☐ Claims _____ are objected to.

6. ☐ Claims _____ are subject to restriction or election requirement.

7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. ☐ Formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).

10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).

12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.

13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. ☐ Other

EXAMINER'S ACTION

The amendment filed September 25, 1995 has been entered. The restriction requirement is withdrawn in view of Applicant's admission that all the inventions are obvious over each other (paper 11).

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 6 is rejected under 35 U.S.C. § 112, first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The vector "pML" is not defined in the specification or the claim. The "how to make" requirement of § 112, first paragraph, can be satisfied for a DNA molecule by disclosing the nucleotide sequence or by a deposit as set forth in 37 CFR 1.801-1.809. The nucleotide sequence of pML has not been disclosed, therefore a deposit is required. If the deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the specific plasmid has been deposited under the Budapest Treaty and that it will be irrevocably and without restriction released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein.

If the deposit is <u>not</u> made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809, applicants may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that

(a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer; and,

(d) a test of the viability of the biological material at the time of deposit (see 37 CFR 1.807); and,

(e) the deposit will be replaced if it should ever become inviable.

Since the specification does not disclose what pML is nor describe its biological properties, one skilled in the art clearly would not know how to use the claimed vector containing portions of pML. Similarly, the claim is indefinite because it does not define what pML or a pML vector sequence is.

Claims 10-12 and 14 are rejected under 35 U.S.C. § 112, first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 10 is indefinite and confusing in its recitation of "293 cells". Literally, this means 293 cells, not a cell line designated "293".

It is believed that "293" designates a cell line. This cell line is not defined or described in the specification. There is also no indication that the cell line is publicly available. Given these shortcomings of the specification, one skilled in the art would not be able to make and use the claimed methods, cell lines, and animals without undue experimentation. This aspect of the rejection under § 112, first paragraph, could be overcome by evidence that the cell line is publicly available and that those skilled in the art would know how to use it.

Furthermore, claim 12 is rejected under § 112, first paragraph, because the specification does not adequately teach how to use the claimed animal. The specification does not disclose the phenotype of any animal infected with the claimed virus and expressing a heterologous gene. The result of expressing a foreign gene in an animal is unpredictable, particularly given the fact that the claim encompasses any animal species and any gene. Without knowing the phenotype of the infected animal, it would require undue experimentation for one skilled in the art to determine how to use it.

Claims 1-17 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically:

Claims 1 and 10 are confusing and unduly alternative in their recitation of "gene(s) and/or gene product(s)".

Claim 1 is indefinite and confusing because the spatial relationship of the vector elements is ambiguous. For example, the splice acceptor and donor site is downstream of the promoter. It could therefore be between the promoter and the cloning site, between the cloning site and the polyadenylation sequence, or downstream of the portion of the adenovirus-5 genome.

Claim 1 is indefinite because the "portion of the adenovirus-5 genome" is not specified. Furthermore, if the vector is a plasmid (i.e., circular), this portion of the Ad-5 genome could be the left end replication and packaging elements, not a separate DNA sequence.

Claim 5 is indefinite in its recitation of "adenovirus nucleotide sequence from 2800-5776". It is not clear what sequence this refers to, nor what base is "1". Furthermore, this sequence would not be identical for different viral isolates.

Claim 7 is indefinite because a plasmid can not literally comprise a map.

Claim 7 is grammatically incorrect in its recitation of "Figures 1(a) or 1(b)".

Claim 8 is indefinite in its recitation of "substantially shown".

Claim 9 is indefinite in its recitation of "a separate site for insertion". Claim 1 already allows more than one insertion site. It is not clear what limitation "separate" provides.

Claim 16 is indefinite and confusing in its recitation of "cDNA insertion site". Since all DNA is chemically equivalent, and equally capable of being cloned into a vector, it is not clear how a "cDNA insertion site" differs from insertion sites for other DNA.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claim 12 is rejected under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over either one of Quantin et al. or Stratford-Perricaudet et al. Both references disclose animals infected with an adenovirus vector. The claim does not recite any anatomical or physiological characteristic which would distinguish the claimed animal

from those of the prior art. Therefore the claim is anticipated by each of the references.

In the event that the claimed animal is not identical to those disclosed by Quantin et al. or Stratford-Perricaudet et al., it is considered that any differences would be the result of minor variation, wherein such variants would have been obvious over the prior art. Thus, the claimed invention as a whole was at least *prima facie* obvious over, if not anticipated by, the prior art.

Claims 1-17 are rejected under 35 U.S.C. § 103 as being unpatentable over any one of Kirshenbaum et al., Quantin et al. or Stratford-Perricaudet et al., in view of Huang et al., Keating et al. and Kabigen. Kirshenbaum et al. disclose a plasmid vector having Ad5 sequences which, when co-transfected with a mutant Ad5 construct into 293 cells, can recombine to produce a replication-incompetent virus containing the plasmid expression cassette (entire document). The replication cassette contains the human CMV promoter, the lacZ gene and the SV40 polyadenylation signal sequence. Within the plasmid, the expression cassette is flanked by Ad5 sequences very similar to those claimed. Kirshenbaum et al. also disclose transfected host cells producing beta-galactosidase. Quantin et al. and Stratford-Perricaudet et al. each disclose similar products and methods, only different promoter and polyadenylation sequences are used in the expression cassette. None of the above three references discloses an expression cassette containing a splice site between the promoter and the gene to be expressed, nor do they disclose the use of the mouse CMV early promoter and mouse beta-globin polyadenylation signal sequences. Huang et al. teach that including a splice site in the 5' untranslated portion of the gene to be expressed resulted in a much higher level of gene expression in several cell lines, including 293 (entire document, e.g. Fig. 2). Keating et al. teach that the murine immediate early CMV promoter produces a high level of gene expression in transfected cells (Table 1, Fig. 1). The Kabigen disclosure teaches that polyadenylation

sequences from rodent beta-globin genes yield efficient RNA processing in transfected cells (p. 5, lines 10-15). Kabigen also discloses vectors which contain additional cloning sites for insertion of additional genes (Figures).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the expression cassette of Kirshenbaum et al., Quantin et al. or Stratford-Perricaudet et al., by including the splice site of Huang et al., the murine CMV promoter of Keating et al., and the mouse beta-globin polyadenylation sequence suggested by Kabigen. One skilled in the art would have been motivated to use these components in the expression cassette, given their recognized value for promoting high level gene expression, and given the expectation that each component would continue to function in its known and expected manner. The specific adenoviral sequence included for recombination is a result-effective variable which would have been routinely optimized by one of ordinary skill in the art. Thus the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bruce Campell, whose telephone number is 703-308-4205. The examiner can normally be reached on Monday-Thursday from 8:30 to 5:00 (Eastern time). The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jacqueline Stone, can be reached on 703-308-3153. The FAX phone number for art unit 1804 is 703-308-4312.

An inquiry of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

Bruce Campell
November 16, 1995

BRUCE R. CAMPELL
PATENT EXAMINER
GROUP 1800